Multiple Brain CRF Receptors: From Molecular Cloning to Circuit Analysis

D.T. Chalmers and E.B. De Souza

Corticotropin-releasing factor (CRF) is the primary factor involved in controlling the release of ACTH from the anterior pituitary and also acts as a neurotransmitter in a variety of brain systems. The actions of CRF are mediated by G-protein coupled membrane bound receptors and a high affinity CRF receptor, CRF_1, has been previously cloned and functionally characterized. Using a degenerate sequence PCR paradigm, we have recently isolated a cDNA encoding a second member of the CRF receptor family, designated CRF_2, which displays approximately 70% homology at the nucleotide level to the CRF_1 receptor and exhibits a distinctive pharmacological profile. The present study utilized *in situ* hybridization histochemistry to localize the distribution of CRF_2 receptor mRNA in brain and pituitary gland and compared this with the distribution of CRF_1 receptor expression. While CRF_1 receptor expression was very high in neocortical, cerebellar and sensory relay structures, CRF_2 receptor expression was generally confined to sub-cortical structures. The highest levels of CRF_2 receptor mRNA in brain were evident within the lateral septal nucleus, the ventromedial hypothalamic nucleus and the choroid plexus. Moderate levels of CRF_2 receptor expression were evident in the olfactory bulb, amygdaloid nuclei, the paraventricular and suraoptic nuclei of the hypothalamus, the inferior colliculus and serotonin-associated raphe nuclei of the midbrain. CRF_2-expressing cells were also evident in the bed nucleus of the stria terminalis, the hippocampal formation and anterior and lateral hypothalmic areas. Within the pituitary gland, CRF_2 receptor mRNA was detectable only at very low levels in scattered cells while CRF_1 receptor mRNA was readily detectable in anterior and intermediate lobes. This heterogeneous distribution of CRF_1 and CRF_2 receptor mRNA suggests distinctive functional roles for each receptor in CRF-related systems.The CRF_1 receptor may be regarded as the primary neuroendocrine pituitary CRF receptor and important in cortical, cerebellar and sensory roles of CRF. The presence of CRF_2 receptors in the PVN may indicate a role for this receptor in modulating CRF neurosecretory neurons in response to stress. Such receptors may be relevant to the proposed role of CRF in ultrashort loop feedback effects on stress-induced ACTH release. In addition, we may speculate that CRF_2 receptors may mediate autonomic and general behavioral actions of central CRF.

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